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ORIGINAL ARTICLE

Design, synthesis and pharmacological evaluation of some novel derivatives of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazine

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Abstract A novel series of 1-{[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazine, compounds **3a–l** have been synthesized. The synthetic work was carried out beginning from 2-acetylfuran through Claisen Schmidt condensation with different types of aromatic aldehyde, affording 1-(furan-2-yl)-3-substitutedphenylprop-2-en-1-ones which on cyclization with hydroxylamine hydrochloride resulted in 3-(furan-2-yl)-5-substitutedphenyl-4,5-dihydro-1,2-oxazole formation. The isoxazolines were subjected to Mannich's reaction in the presence of N-methyl piperazine to produce the desired product. The chemical structures of the compounds were proved by IR, ^{1}H NMR, ^{13}C-NMR and Mass spectrometric data. The antidepressant activities of the compounds were investigated by Porsolt's behavioral despair (forced swimming) test on albino mice. Moreover, the antianxiety activity of the newly synthesized compounds was investigated by the plus maze method. Compounds **3a** and **3k** reduced the duration of immobility times of 152.00–152.33% at 10 mg/kg dose level and compounds **3a** and **3k** have also shown significant antianxiety activity.

1. Introduction

Considerable approaches have passed during the past two decades in the pharmacological treatment of anxiety and depression. Depression is a state of low mood and aversion to activity that can have a negative effect on a person's thoughts, behavior, feelings, world view and physical well-being. World Health Organization calculates that by 2020 depression will be the second most disabling condition in the world (Rozas,

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2009). Based on these statistics, it is clear that there is a demand for new drug candidates in the treatment of depression (Kennedy and Rizvi, 2009). Contempt these advances, unmet medical needs still survive for the treatment of anxiety and depression. Among the deficiencies of modern drugs are slow onset of action, lack of success in refractory patients, and presence of unwanted gastrointestinal and sexual side effects. In addition, anxiety and depression are conceived to be different neuropsychiatric diseases, there is considerable overlap among the clinical symptoms of these disorders and differential diagnosis is often difficult (Tyrer, 1992). Anxiety often coexists with depression or may precede the development of depressive symptoms (Nutt and Glue, 1989) and anxiety and depression may be biochemically colligated since there are many similarities in the neurological substrates thought to play a role in these diseases, (Glennon and Dukat, 1995; Heninger, 1995; Sleight et al., 1991; Siever et al., 1991; Perregaard et al., 1993; Glennon, 1990; Zifa and Fillion, 1992) including a recent report describing a polymorphism in the serotonin transporter gene associated with both anxiety and depression-related personality traits (Lesch, 1998). In accession, anxiolytic agents may have utility in treating depression, (Charney et al., 1990) and there is developing clinical evidence that antidepressants may be effective in treating generalized anxiety disorder (Rickels et al., 1993). Monoamine oxidase inhibitors (MAOIs) initially were the first line medications in the treatment of depressive illness, however, due to serious side effects, the interest in these drugs lessened (Coutts et al., 1986). Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors have historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) have failed. When the two isoforms, MAO-A and MAO-B, were discovered, interest was renewed in their potential therapeutic employment, and several new generations of selective MAO inhibitors have evolved (Youdim et al., 2006). There is growing evidence for a beneficial therapeutic effect of MAO-B specific inhibitors in the treatment of patients suffering with early stages of Parkinson's disease (Youdim et al., 2006). There is an increased interest in the development of potent and selective MAOIs, due to this increased consciousness of neurological disease states. Reversible selective MAO-A inhibitions are employed as antidepressant and antianxiety drugs (Rudorfer and Potter, 1989), and selective MAO-B inhibitors are coadjuvant in the treatment of Parkinson's disease and perhaps also in Alzheimer's disease (Wouters, 1998; Tetrud and Langston, 1989). Isocarboxazide is an irreversible and nonselective monoamine oxidase inhibitor (MAOI) of the hydrazine chemical class employed as an antidepressant and anxiolytic (Fagervall and Ross, 1986). A number of isoxazole derivatives are experienced to have antidepressant, antianxiety (Garvey et al., 1994; Wagner et al., 2004; Andres et al., 2007; Ignacio and Gil, 2004, 2007, 2008; Sheeja Mary et al., 2011) anti-stress (Maurya et al., 2011), anticonvulsant (Balalaie et al., 2000), antiviral (Lee et al., 2009), anti-inflammatory (Dannahardt et al., 2000), anti-inflammatory and analgesic activities (Jayashankar et al., 2009).

The target compounds were designed based on the fact that isocarboxazide develops an inhibition of monoamine oxidase in *in-vitro* and *in-vivo* studies, and isocarboxazide is an isoxazole derivative. Additionally, docking analysis facilitates understanding the nature of interactions governing the binding of the designed molecule with the MAO-A enzyme. On the basis of this context, the present work has been aimed to synthesize some novel 1-{[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine derivatives. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. Their antidepressant and anxiolytic activities were evaluated by the FST and the plus maze methods respectively. To evaluate their receptor binding study, compounds with a diversified MAO functional profile were chosen and examined using common behavioral tests for predicting antidepressant and/or anxiolytic like activities in mice. Furthermore, molecular modeling studies using synthesized isoxazole derivatives were performed to predict the preferred binding modes of compounds with MAO-A.

2. Experimental

2.1. Chemistry

All the chemicals used were of laboratory grade and procured from E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points were determined by the open tube capillary method and are uncorrected. The thin layer chromatography (TLC) plates (silica gel G) were used to justify the purity of commercial reagents used, compounds synthesized and to monitor the reaction progress. Two different solvent systems: toluene:ethyl acetate:formic acid (5:4:1) and benzene:acetone (9:1) were used to run the TLC and spots were located under iodine vapors/UV light. An IR spectrum was obtained on a Perkin–Elmer 1720 FT-IR spectrometer (KBr Pellets). Elemental analyses were carried out on a Perkin–Elmer 2400 analyzer (USA) and were found within $\pm 0.5\%$ of the theoretical values. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker 400 and 75 MHz spectrometer, respectively, using tetramethylsilane (TMS) as the internal reference (chemical shift was measured in δ ppm). Mass spectra (ESI-Q-TOF) were measured on a Waters mass spectrometer with an ESI (Electron spray ionization) source.

2.2. General procedure for the preparation of 1-(furan-2-yl)-3-substituted phenylprop-2-en-1-ones (*1a–l*)

2.2.1. Step I. Preparation of chalcones facilitates Claisen Schmidt condensation

A mixture of 2-acetylfuran (0.01 mol) and appropriate aldehydes (0.01 mol) in oxygen-free methanol (30 mL) was stirred at room temperature in the presence of base (aqueous solution of potassium hydroxide 40%; 15 mL) till completion of the reaction. The reaction mixture was kept overnight at room temperature and then poured into crushed ice followed by neutralization with HCl. The solid separated was filtered, dried and crystallized from ethanol. The purity of the chalcones was checked by TLC.

2.2.2. Step II. Cyclization with hydroxylamine hydrochloride

To a solution of compounds **1a–l** (0.01 mol) in absolute ethanol (50 ml), dry pyridine (1 ml) and hydroxylamine hydrochloride (0.01 mol) were added. The reaction mixtures were refluxed for 8–10 h at 80 °C and cooled in a refrigerator overnight. The solvent was evaporated, and reaction mixture was then poured into ice-cold water. The obtained precipitate

was filtered, washed with water and dried in air. The product was recrystallized from methanol.

The IR spectrum of compound (**2a**) showed an absorption peak at 1352 cm^{-1} due to C–O–N, 1656 cm^{-1} for C=N and 1052 cm^{-1} for C–O–C stretching vibration. The structure was further conformed by its ^{1}H NMR spectrum, which showed two double doublets at δ 3.56 and δ 3.71 for CH_2 protons of isoxazoline ring. The CH proton at C-5 of isoxazoline was obtained as a triplet at δ 6.04. Thus, disappearance of signals of the olefinic protons and appearance of CH_2 and CH proton signals in the spectrum confirmed the formation of isoxazoline ring. The mass spectrum of the compound **2a** showed a molecular ion peak M^+ at m/z 213 corresponding to molecular formula $C_{13}H_{11}NO_2$.

*2.2.3. Step III. Mannich's reaction involved for the preparation of final derivative (**3a–l**)*

To a solution of compounds **2a–l** (0.01 mol) in methanol (50 ml), formaldehyde (0.02 mol) and 1-methyl piperazine (0.01 mol) were added. The reaction mixture was refluxed for 6 h. the solvent was distilled off, and the residue was poured into ice water. The precipitated solid was filtered off, dried and recrystallized from appropriate solvents. All the synthesized compounds were purified by suitable solvents. Purity of compounds was checked by TLC. The physico-chemical data were presented in Table 1.

2.3. Characterization of synthesized derivatives

*2.3.1. 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3a**)*

FT-IR (KBr pellet) cm^{-1}: 3126 (aromatic C–H stretch), 1686 (C=N stretch), 1362 (C–O–N stretch), 1048 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.89–7.72 (t, 3H, furan), 7.61–7.03 (m, 5H, Ar–H), 5.34 (d, 1H, isoxazoline, J = 6.7 Hz), 4.29 (m, 1H, isoxazoline), 3.41 (d, 2H, J = 6.2 Hz (CH_2–N), 3.27–2.54 (t, 8H, J = 4.6 Hz CH_2–N–CH_2 piperazine), 2.51 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.92 (C), 145.40 (C), 142.46 (C), 139.57 (C), 129.74 (2C), 129.24 (C), 128.99 (2C), 119.43 (C), 104.14 (C), 84.53 (C), 53.76 (2C), 51.93 (2C), 51.82 (C), 46.76 (C); ESI-MS: m/z 325 (M+); Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13, H, 7.12, N, 12.91, Found C, 70.12, H, 7.11, N, 12.93%.

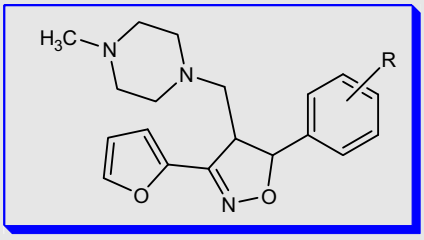
*2.3.2. 1-{[3-(furan-2-yl)-5-(4-methylphenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3b**):*

FT-IR (KBr pellet) cm^{-1}: 3116 (aromatic C–H stretch), 1680 (C=N stretch), 1359 (C–O–N stretch), 1052 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.80–7.62 (t, 3H, furan), 7.41–7.12 (m, 4H, Ar–H), 5.38 (d, 1H, isoxazoline J = 6.9 Hz), 4.20 (m, 1H, isoxazoline), 3.47 (d, 2H, J = 6.0 Hz (CH_2–N), 3.37–2.48 (t, 8H, J = 4.3 Hz CH_2–N–CH_2 piperazine), 2.86 (s, 3H, Ar–CH_3), 2.48 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 150.02 (C), 146.34 (C), 142.36 (C), 139.51 (C), 130.14 (2C), 129.20 (C), 129.09 (2C), 119.40 (C), 104.24 (C), 84.13 (C), 53.70 (2C), 52.13 (2C), 52.42 (C), 46.16 (C); ESI-MS: m/z 339 (M+); Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 70.77, H, 7.42, N, 12.38, Found C, 70.74, H, 7.38, N, 12.35%.

*2.3.3. 1-{[3-(furan-2-yl)-5-(2-chlorophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3c**):*

FT-IR (KBr pellet) cm^{-1}: 3096 (aromatic C–H stretch), 1678 (C=N stretch), 1342 (C–O–N stretch), 1068 (furan C–O–C

Table 1 Physicochemical parameters of the synthesized compounds (**3a–l**).



Compd. No.	R	Yield[a] (%)	m.p. (°C)	Mol. formula	Mol. wt	log P[b]	R_f[c]
3a	H	68	122–123	$C_{19}H_{23}N_3O_2$	325.40	0.87 ± 0.64	0.39
3b	4-CH_3	60	134	$C_{20}H_{25}N_3O_2$	339.43	1.33 ± 0.64	0.43
3c	2-Cl	58	142	$C_{19}H_{22}ClN_3O_2$	359.84	1.46 ± 0.64	0.36
3d	4-Cl	54	138–140	$C_{19}H_{22}ClN_3O_2$	359.84	1.46 ± 0.64	0.42
3e	4-Br	68	108	$C_{19}H_{22}BrN_3O_2$	404.30	1.64 ± 0.66	0.37
3f	4-F	65	94–95	$C_{19}H_{22}FN_3O_2$	343.39	0.92 ± 0.66	0.41
3g	4-OH	50	70–72	$C_{19}H_{23}N_3O_3$	341.40	0.13 ± 0.64	0.38
3h	4-OCH_3	64	102	$C_{20}H_{25}N_3O_3$	355.43	0.78 ± 0.64	0.39
3i	4-NH_2	66	128–129	$C_{19}H_{24}N_4O_2$	340.41	−0.41 ± 0.64	0.41
3j	4-NO_2	72	138	$C_{19}H_{22}N_4O_4$	370.40	0.60 ± 0.64	0.37
3k	4-$N(CH_3)_2$	69	142–144	$C_{21}H_{28}N_4O_2$	368.47	0.98 ± 0.65	0.38
3l	3,4-$(OCH_3)_2$	56	116	$C_{21}H_{27}N_3O_4$	385.45	0.61 ± 0.65	0.39

[a] After recrystallization from ethanol.
[b] ACD/CLogP 12.0 software.
[c] Toluene:ethyl acetate:formic acid (5:4:1).

stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.69–7.52 (t, 3H, furan), 7.36–7.13 (m, 4H, Ar–H), 5.64 (d, 1H, J = 7.0 Hz isoxazoline), 4.16 (m, 1H, isoxazoline), 3.48 (d, 2H, J = 6.2 Hz (CH_2–N), 3.22–2.34 (t, 8H, J = 4.7 Hz CH_2–N–CH_2 piperazine), 2.58 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 150.02 (C), 141.48 (C), 141.36 (C), 136.87 (C), 129.84 (2C), 129.44 (C), 128.69 (2C), 119.39 (C), 103.94 (C), 83.98 (C), 54.06 (2C), 51.63 (2C), 51.64 (C), 47.06 (C); ESI-MS: m/z 359 (M^+) and 361 (M + 2); Anal. Calcd. for $C_{19}H_{22}ClN_3O_2$: C, 63.42, H, 6.16, N, 11.68, Found C, 63.39, H, 6.18, N, 11.65%.

2.3.4. 1-{[3-(furan-2-yl)-5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (3d)

FT-IR (KBr pellet) cm^{-1}: 3122 (aromatic C–H stretch), 1666 (C═N stretch), 1336 (C–O–N stretch), 1064 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.68–7.32 (t, 3H, furan), 7.46–6.93 (m, 4H, Ar–H), 5.53 (d, 1H, J = 6.2 Hz isoxazoline), 4.32 (m, 1H, isoxazoline), 3.51 (d, 2H, J = 6.7 Hz (CH_2–N), 3.43–2.64 (t, 8H, J = 5.0 Hz CH_2–N–CH_2 piperazine), 2.56 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 150.02 (C), 142.64 (C), 142.24 (C), 140.05 (C), 130.14 (2C), 128.34 (C), 128.29 (2C), 120.13 (C), 103.94 (C), 84.63 (C), 53.95 (2C), 52.13 (2C), 51.92 (C), 47.12 (C); ESI-MS: m/z 359 (M^+) and 361 (M + 2); Anal. Calcd. for $C_{19}H_{22}ClN_3O_2$: C, 63.42, H, 6.16, N, 11.68, Found C, 63.40, H, 6.18, N, 11.65%.

2.3.5. 1-{[3-(furan-2-yl)-5-(4-bromophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3e**)

FT-IR (KBr pellet) cm^{-1}: 3162 (aromatic C–H stretch), 1678 (C═N stretch), 1365 (C–O–N stretch), 1056 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.69–7.42 (t, 3H, furan), 7.58–7.10 (m, 4H, Ar–H), 5.29 (d, 1H, J = 6.3 Hz isoxazoline), 4.36 (m, 1H, isoxazoline), 3.48 (d, 2H, J = 6.5 Hz (CH_2–N), 3.43–2.39 (t, 8H, J = 4.2 Hz CH_2–N–CH_2 piperazine), 2.54 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.72 (C), 146.02 (C), 142.49 (C), 139.71 (C), 130.14 (2C), 129.41 (C), 128.86 (2C), 120.03 (C), 104.18 (C), 84.64 (C), 54.13 (2C), 52.03 (2C), 51.79 (C), 47.06 (C); ESI-MS: m/z 404 (M^+) and 406 (M + 2); Anal. Calcd for $C_{19}H_{22}BrN_3O_2$: C, 56.44, H, 5.48, N, 10.39, Found C, 56.40, H, 5.52, N, 10.43%.

2.3.6. 1-{[3-(furan-2-yl)-5-(4-fluorophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3f**)

FT-IR (KBr pellet) cm^{-1}: 3122 (aromatic C–H stretch), 1676 (C═N stretch), 1366 (C–O–N stretch), 1052 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.92–7.70 (t, 3H, furan), 7.58–7.23 (m, 4H, Ar–H), 5.24 (d, 1H, J = 6.4 Hz isoxazoline), 4.32 (m, 1H, isoxazoline), 3.37 (d, 2H, J = 6.1 Hz (CH_2–N), 3.22-2.57 (t, 8H, J = 4.5 Hz CH_2–N–CH_2 piperazine), 2.55 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (DMSO-d_6): δ (ppm) 149.99 (C), 145.36 (C), 142.86 (C), 140.07 (C), 130.04 (2C), 129.44 (C), 128.89 (2C), 119.49 (C), 104.30 (C), 84.33 (C), 54.16 (2C), 52.10 (2C), 52.00 (C), 46.77 (C); ESI-MS: m/z 343 (M+); Anal. Calcd. for $C_{19}H_{22}FN_3O_2$: C, 66.45, H, 6.46, N, 12.24, Found C, 66.43, H, 6.48, N, 12.25%.

2.3.7. 1-{[3-(furan-2-yl)-5-(4-hydroxyphenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3g**)

FT-IR (KBr pellet) cm^{-1}: 3096 (aromatic C–H stretch), 1700 (C═N stretch), 1364 (C–O–N stretch), 1052 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 8.47 (s, 1H, Ar–OH), 7.80–7.62 (t, 3H, furan), 7.20–6.98 (m, 4H, Ar-H), 5.38 (d, 1H, J = 6.2 Hz isoxazoline), 4.31 (m, 1H, isoxazoline), 3.36 (d, 2H, J = 6.5 Hz (CH_2–N), 3.29–2.63 (t, 8H, J = 4.7 Hz CH_2–N–CH_2 piperazine), 2.49 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.87 (C), 145.45 (C), 142.66 (C), 139.53 (C), 129.64 (2C), 129.18 (C), 129.00 (2C), 119.39 (C), 104.10 (C), 84.48 (C), 53.68 (2C), 52.13 (2C), 51.78 (C), 46.72 (C); ESI-MS: m/z 341 (M+); Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84, H, 6.79, N, 12.31, Found C, 66.80, H, 6.81, N, 12.29%.

2.3.8. 1-{[3-(furan-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (3h)

FT-IR (KBr pellet) cm^{-1}: 3143 (aromatic C–H stretch), 1676 (C═N stretch), 1367 (C–O–N stretch), 1043 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.72–7.68 (t, 3H, furan), 7.56–7.30 (m, 4H, Ar–H), 5.30 (d, 1H, J = 6.7 Hz isoxazoline), 4.33 (m, 1H, isoxazoline), 4.05 (s, 3H, Ar–OCH_3), 3.33 (d, 2H, J = 6.2 Hz (CH_2–N), 3.24–2.68 (t, 8H, J = 4.3 Hz CH_2–N–CH_2 piperazine), 2.53 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.88 (C), 145.50 (C), 142.56 (C), 139.67 (C), 130.11 (2C), 129.33 (C), 128.87 (2C), 119.49 (C), 103.94 (C), 84.59 (C), 53.67 (2C), 52.14 (2C), 51.88 (C), 46.63 (C); ESI-MS: m/z 355 (M+); Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58, H, 7.09, N, 11.82, Found C, 67.55, H, 7.11, N, 1.79%.

2.3.9. 1-{[3-(furan-2-yl)-5-(4-aminophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3i**)

FT-IR (KBr pellet) cm^{-1}: 3136 (aromatic C–H stretch), 1667 (C═N stretch), 1360 (C–O–N stretch), 1046 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.58–7.32 (t, 3H, furan), 7.48–7.00 (m, 4H, Ar–H), 5.43 (d, 1H, J = 6.8 Hz isoxazoline), 5.01 (s, 2H, Ar–NH_2), 4.27 (m, 1H, isoxazoline), 3.40 (d, 2H, J = 6.3 Hz (CH_2–N), 3.30–2.59 (t, 8H, J = 4.4 Hz CH_2–N–CH_2 piperazine), 2.55 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.82 (C), 145.45 (C), 142.43 (C), 139.62 (C), 129.70 (2C), 129.33 (C), 129.00 (2C), 119.39 (C), 104.17 (C), 84.58 (C), 53.67 (2C), 51.90 (2C), 51.85 (C), 46.68 (C); ESI-MS: m/z 340 (M+); Anal. Calcd. for $C_{19}H_{24}N_4O_{2:}$ C, 67.04, H, 7.11, N, 16.46, Found C, 67.01, H, 7.09, N, 16.43%.

2.3.10. 1-{[3-(furan-2-yl)-5-(4-nitrophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3j**)

FT-IR (KBr pellet) cm^{-1}: 3137 (aromatic C–H stretch), 1678 (C═N stretch), 1358 (C–O–N stretch), 1050 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.73–7.32 (t, 3H, furan), 7.60–7.02 (m, 4H, Ar–H), 5.36 (d, 1H, J = 6.2 Hz isoxazoline), 4.25 (m, 1H, isoxazoline), 3.40 (d, 2H, J = 6.5 Hz (CH_2–N), 3.32–2.47 (t, 8H, J = 4.6 Hz CH_2–N–CH_2 piperazine), 2.53 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.91 (C), 145.37 (C), 142.41 (C), 139.60 (C), 129.65 (2C), 129.34 (C), 128.94 (2C), 119.39 (C), 104.17 (C), 84.57 (C), 53.70

(2C), 51.89 (2C), 51.72 (C), 46.66 (C); ESI-MS: *m/z* 370 (M+); Anal. Calcd. for $C_{19}H_{22}N_4O_4$: C, 61.61, H, 5.99, N, 15.13, Found C, 61.59, H, 5.89, N, 15.10%.

*2.3.11. 1-{[3-(furan-2-yl)-5-(4-N,N-dimethylaminophenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3k**)*

FT-IR (KBr pellet) cm^{-1}: 3120 (aromatic C–H stretch), 1680 (C=N stretch), 1360 (C–O–N stretch), 1045 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.80–7.70 (t, 3H, furan), 7.60–7.00 (m, 4H, Ar–H), 5.33 (d, 1H, J = 6.3 Hz isoxazoline), 4.30 (m, 1H, isoxazoline), 3.43 (d, 2H, J = 6.7 Hz (CH_2–N), 3.30-2.51 (t, 8H, J = 4.2 Hz CH_2–N–CH_2 piperazine), 2.51 (s, 3H, N–CH_3 piperazine), 2.27 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.90 (C), 145.42 (C), 142.49 (C), 139.60 (C), 129.75 (2C), 129.28 (C), 128.97 (2C), 119.41 (C), 104.13 (C), 84.56 (C), 53.72 (2C), 51.95 (2C), 51.80 (C), 46.79 (C); ESI-MS: *m/z* 368 (M+); Anal. Calcd. for $C_{21}H_{28}N_4O_2$: C, 68.45, H, 7.66, N, 15.21, Found C, 68.47, H, 7.64, N, 15.19%.

*2.3.12. 1-{[3-(furan-2-yl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3l**)*

FT-IR (KBr pellet) cm^{-1}: 3123 (aromatic C–H stretch), 1682 (C=N stretch), 1367 (C–O–N stretch), 1045 (furan C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 7.90–7.65 (t, 3H, furan), 7.66–7.00 (m, 4H, Ar–H), 5.39 (d, 1H, J = 6.5 Hz isoxazoline), 4.34 (m, 1H, isoxazoline), 3.81 (s, 6H, 2 × O–CH_3), 3.43 (d, 2H, J = 6.7 Hz (CH_2–N), 3.34–2.48 (t, 8H, J = 4.9 Hz CH_2–N–CH_2 piperazine), 2.54 (s, 3H, N–CH_3 piperazine); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 149.89 (C), 145.39 (C), 142.49 (C), 139.59 (C), 129.78 (2C), 129.29 (C), 128.95 (2C), 119.40 (C), 104.10 (C), 84.56 (C), 53.72 (2C), 51.91 (2C), 51.80 (C), 46.73 (C); ESI-MS: *m/z* 385 (M+); Anal. Calcd. for $C_{21}H_{27}N_3O_4$: C, 65.44, H, 7.06, N, 10.90, Found C, 65.47, H, 7.07, N, 10.93%.

2.4. Antidepressant activity (forced swim test in mice)

Swiss albino mice (20–24 g) were used for the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On the test day mice were dropped once at a time into a Plexiglass cylinder containing 10 cm of water at 23–25 °C (Porsolt et al., 1977). On the testing day, mice were assigned into different groups (n = 6 for each group). The synthesized compounds were screened for their antidepressant activity using Porsolt's behavioral despair (forced swimming) test. Briefly, the mice were individually placed in a glass cylinder (25 cm high; 10 cm in diameter) containing 6 cm of water kept at 23–25 °C, and were left therein for 6 min. The synthesized compounds (10 mg kg^{-1}), and imipramine, as a reference antidepressant drug (10 mg kg^{-1}) were suspended in a 1% aqueous solution of Tween 80. The drugs were injected intraperitoneally (ip) in a standard volume of 0.5 ml/20 g body weight, 1 h prior to the test. Control animals received 1% aqueous solution of Tween 80. Then, the mice were dropped individually into the Plexiglass cylinder and left in the water for 6 min. For the first 2 min of initial vigorous struggling the animals were immobile. Immobility time is the time spent by mice floating in water without struggling, making only those movements necessary to keep the head above the water. The total duration of immobility was recorded during the last 4 min of the 6 min test session. The data of antidepressant activity are given in Table 2.

2.5. Anxiolytic activity (elevated plus maze test in mice)

Swiss albino mice, weighing 20–24 g each, were selected from the stock colony maintained in the central animal facility with free access to food and water. Animals were maintained in an air-conditioned room. The room was maintained at 25 ± 2 °C with natural daytime. Concentration of each compound (10 mg/kg) was used in the form

Table 2 Antidepressant activity of the newly synthesized compounds (forced swim test in mice).

Compounds	Antidepressant activity	
	Immobility time (s) (mean ± SEM)	Change from control (%)
3a	152.33 ± 0.84[b]	−8.88
3b	164.50 ± 0.76	−1.60
3c	163.17 ± 0.60[a]	−2.39
3d	160.50 ± 0.76[b]	−3.99
3e	163 ± 0.93[a]	−2.49
3f	162.83 ± 0.70[a]	−2.60
3g	158.50 ± 0.76[b]	−5.19
3h	156.50 ± 1.47[b]	−6.38
3i	166.83 ± 1.07	−0.20
3j	157.67 ± 1.22[b]	−5.68
3k	152 ± 0.57[b]	−9.07
3l	162 ± 0.89[b]	−3.09
Imipramine	149.67 ± 0.84[b]	−10.47
Control	167.17 ± 0.60	–

Values represent the mean ± SEM (n = 6).
[a] Significant compared to control (Dunnet's test; $p < 0.05$).
[b] Most significant compared to control (Dunnet's test; $p < 0.01$).

Table 3 Anti anxiety activity of the newly synthesized compounds (elevated plus maze test in mice).

Compounds	% Preference to open arm	Open arm	
		No. of entries (mean ± SEM)	Average time spent (mean ± SEM)
3a	14.17	4.33 ± 0.42[b]	42.50 ± 0.76[b]
3b	6.00	2.16 ± 0.30	18 ± 0.57
3c	6.83	2.33 ± 0.21	20.50 ± 0.76[b]
3d	11.50	3.33 ± 0.21[a]	34.50 ± 0.76[b]
3e	9.83	3.50 ± 0.34[a]	29.50 ± 0.76[b]
3f	6.94	3 ± 0.36 ns	20.83 ± 0.94[b]
3g	12.17	3.83 ± 0.30[b]	36.50 ± 0.76[b]
3h	6.39	3.50 ± 0.22[a]	19.16 ± 0.79[a]
3i	6.33	2.50 ± 0.22	19 ± 0.57
3j	6.50	2.66 ± 0.33	19.50 ± 0.99[a]
3k	15.11	4.16 ± 0.30[b]	45.33 ± 0.66[b]
3l	5.72	2.33 ± 0.42	17.16 ± 0.94
Control	5.33	2 ± 0.25	16.0 ± 0.57
Diazepam	19.50	4.83 ± 0.47[b]	58.50 ± 0.76[b]

Values represent the mean ± SEM ($n = 6$).
[a] Significant compared to control (Dunnet's test; $p < 0.05$).
[b] Most significant compared to control (Dunnet's test; $p < 0.01$).

of freshly prepared suspensions in 1% tween 80. All solutions were prepared freshly on test days and given intraperitoneally (ip) in a volume of 0.5 ml/20g body weight of mice. The experimental animals were treated with Diazepam (2 mg/ kg, $n = 6$), or the compounds (10 mg/kg) 60 min before evaluation in the maze. The control group was given saline with 1% tween 80.

Plus maze for mice (Moser, 1989; Rabbani et al., 2004; Pellow et al., 1985; Kulkarni, 2002) consisted of two open (16×5 cm^2) and two closed arms ($16 \times 5 \times 12$ cm^3) facing each other with an open roof. The entire maze is elevated to a height of 25 cm. In the test, mice were individually examined in 5 min sessions in this apparatus. Each mouse was placed in the central platform facing one open arm. The numbers of entries into open and closed arms and the time spent in the respective arms were recorded during a 5 min period. The percentage of time spent in the open arms [(open/open + closed) × 100] was calculated for each mouse. The results of EPM have been summarized in Table 3.

2.6. Neurotoxicity

The rotarod test was used to evaluate neurotoxicity. The animal was placed on a 1 inch diameter knurled wooden rod rotating at 6 rpm. Normal mice remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min.

2.7. Statistical analysis

Results are expressed as mean SEM; n represents the number of animals. Data obtained from pharmacological experiments were analyzed by one way analysis of variance (ANOVA) followed by Dunnet's test and used to evaluate the results, using InStat GraphPad (version 3.06, GraphPad Software Inc., San Diego, CA, USA). A p-value of less than 0.05 was considered statistically significant.

2.8. Docking study

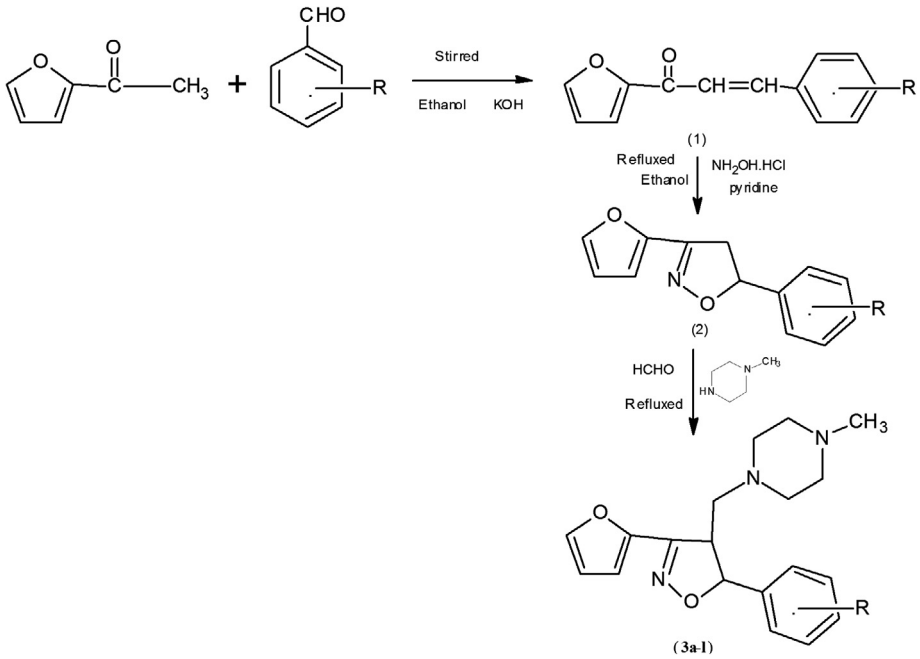
The docking analysis of most active molecule was performed using Maestro, version 9.2 implemented from Schrodinger molecular modeling suite. The molecules were sketched in the 3D format using build panel and LigPrep module was used to produce low-energy conformers. The crystal structure of MAO-A (PDB ID: 2BXR) was obtained from protein data bank. The protein was prepared by giving preliminary treatment like adding hydrogen, adding missing residues, refining the loop with prime and finally minimized by using OPLS-2005 force field. Grid for molecular docking was generated with bound co-crystallized ligand. Molecules were docked using Glide in extra-precision mode, with up to three poses saved. Ligands were kept flexible by producing the ring conformations and by penalizing non-polar amide bond conformations, whereas the receptor was kept rigid throughout the docking studies. All other parameters of the Glide module were maintained at their default values. The lowest energy conformation was selected for the prediction of ligand interactions with the active sites of MAO-A.

3. Results and discussion

3.1. Chemistry

The reaction routes for the synthesis of the title compounds were described in scheme 1. Structures, yields and melting points of the compounds are listed in Table 1. All spectral data are in accordance with expected structures. The IR spectra of the compounds provided information of isoxazoline C=N stretching (1666–1700 cm^{-1}), isoxazoline C–O–N stretching (1336–1367 cm^{-1}), aromatic C–H stretching (3096–3162 cm^{-1}), and furan C–O–C stretching (1043–1068 cm^{-1}) bands.

The ^{1}H NMR spectra of the compound (**3a**) δ (ppm) show: 7.89–7.72 (t, 3H, furan); 7.61–7.03 (m, 5H, Ar–H); 5.34 (d, 1H,



Scheme 1 Synthetic route for the preparation of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl Piperazine derivatives **(3a-l)**.

isoxazoline, $J = 6.7$ Hz); 4.29 (m, 1H, isoxazoline); 3.41 (d, 2H, $J = 6.2$ Hz (CH_2–N), 3.27-2.54 (t, 8H, $J = 4.6$ Hz CH_2–N–CH_2 piperazine), 2.51 (s, 3H, N–CH_3 piperazine). In the mass spectra of the compounds, molecular ions (M+) were observed.

3.2. Biology

The forced swimming test is a behavioral test used to predict the efficacy of antidepressant treatments (Porsolt et al., 1977). It is used efficaciously in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants. It has a strong predictive value for antidepressant potency in humans. The obtained data on the antidepressant activity of the compounds and reference drug are given in Table 2. In the present study, 1-{[3-(furan-2-yl)-5-(4-N,N-dimethylamino phenyl)-4,5-di hydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3k**) and 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4 methyl piperazine (**3a**) significantly reduced the duration of immobility times at 10 mg kg^{-1} dose level when compared to control ($p < 0.05$, Table 2). All the substitutions were made at the phenyl ring to evaluate their structure activity relationship. The antidepressant activity of the synthesized compounds having p-N, N-$(CH_3)_2$ (**3k**), un-substituted phenyl (**3a**) and p-O–CH_3 (**3h**) groups at the para position of phenyl ring was significantly reduced (immobility time −6.38 to −9.07%). However, the para substituted compounds like p-CH_3 (**3b**), p-Cl (**3d**), p-Br (**3e**), p-F (**3f**) and p-NH_2 (**3i**) groups moderately decreased the immobility time with respect to control.

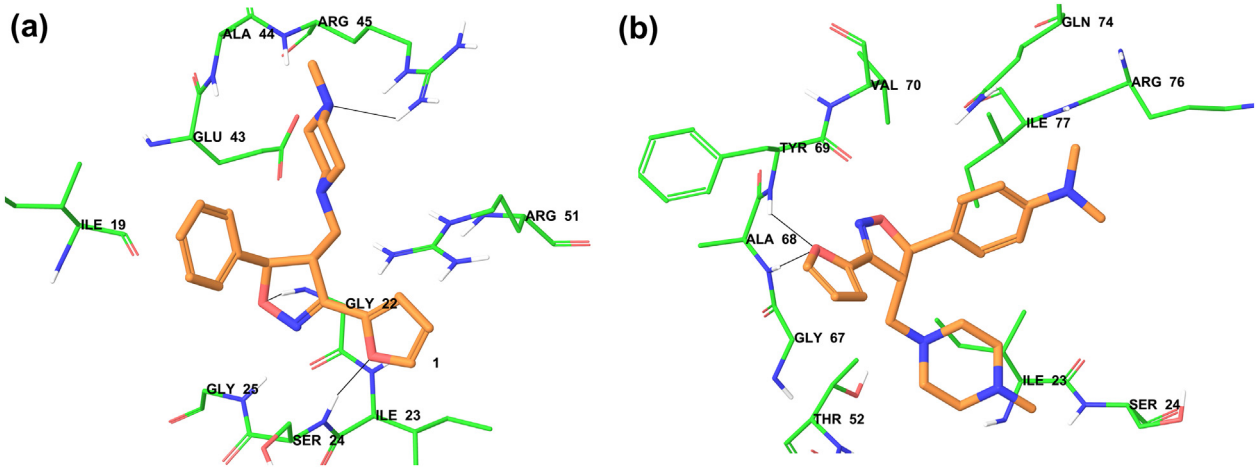


Figure 1 Binding pattern and interaction of **3a** (a) and **3k** (b) at the binding site of MAO-A enzyme.

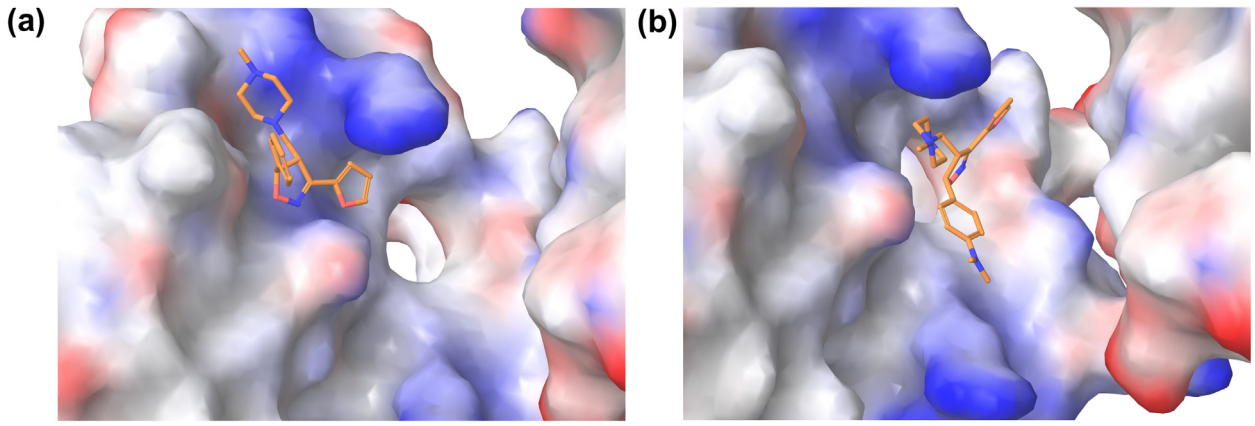


Figure 2 Docking orientations of **3a** (a) and **3k** (b) at the binding surface of the enzyme.

The antianxiety activities of the synthesized compounds were also investigated, and results from these experiments are shown in Table 3. Compounds **3a, 3g** and **3k** were found to have most potent anxiolytic activity using the elevated plus maze method. Neurotoxicity was observed in none of the synthesized compounds in the dose of 10 mg kg^{-1}.

3.3. Docking analysis

Docking analysis was performed using both most active molecules. *In silico* modeling studies predicted good binding modes of **3a** and **3k** with the binding site of MAO-A enzyme. Molecules are interacting by good hydrogen bonding with the active site residues of protein. Molecule **3a** is making two hydrogen bonds with Gly-22, Ser-24 and Arg-45 while, molecule **3k** is interacting with Ala-68 and Tyr-69 by hydrogen bonding (Fig. 1). Both of the molecules were well occupied in the binding site pocket of the enzyme. Fig. 2 represents the binding orientation of both molecules at the binding site surface of the protein.

4. Conclusion

The research study reports the successful synthesis of compounds **3a–l**. The synthesized compounds **3k** and **3a** have shown substantial anti-depressant activity, and also due to the presence of a furyl substituent at the third position and phenyl substituent at the fifth position of the isoxazoline ring (**3k** and **3a**) possess remarkable anti-anxiety activity. Therefore, they seem to be extremely anticipating compounds for their antianxiety activities. The synthesis studies should be extended concerning this group of compounds followed by further clinical studies. The molecular modeling studies also predicted good binding interactions of most active molecules with the MAO-A. Therefore, it can be safely concluded that compounds **3k** and **3a** would represent a useful model for further investigation in the development of a new class of dual anti-depressant and anti-anxiety agents.

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